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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 09/839,946 | 04/19/2001 | L. David Williams | MVIEWD.1A2DV1 | 5256 |

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| EXAMINER | |
|---|---|
| SAIDHA, TEKCHAND | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 12/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

| Advisory Action Before the Filing of an Appeal Brief | Application No. 09/839,946 | Applicant(s) WILLIAMS ET AL. | |
|---|---|---|---|
| | Examiner Tekchand Saidha | Art Unit 1652 | |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 20 October 2005 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☐ The period for reply expires _____months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☒ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: 50-59.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: see Office Action, attached here.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

**Advisory Action**

1. Applicants' amendment after-final and arguments filed on October 20, 2005 is acknowledged. Claims 1-49 & 60-76 are cancelled.

2. Declaration of Merry R. Sherman Under 37 C.F.R. 1.132, filed on May 25, 2005 is reconsidered.

3. Any objection or rejection of record which is not expressly repeated in this Office Action has been overcome by Applicant's response and withdrawn.

4. Claims 50-59 drawn to an isolated tetrameric mammalian uricase are pending and under consideration in this Office Action.

5. Applicants' response and Declaration of Merry R. Sherman filed May 25, 2005 and arguments filed as per the amendment after-final have been fully considered but they are not deemed to be persuasive as explained following the rejections.

6. ***Claim Rejections - 35 U.S.C. § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 50-53 are rejected under 35 U.S.C. 102(b) as anticipated by Lee et al. [Science 239, 1288-1291 (1988), IDS, previously cited].

Lee et al. (1988) teach the recombinant production of full length amino acid sequence of porcine Urate oxidase (uricase) which is tetrameric and is substantially pure. Mammalian uricase is disclosed as a tetramer with subunit size of 32,000 Daltons (page 1288, column 2,first paragraph after the abstract). The reference further teaches purification to **homogeneity** of Porcine and murine urate oxidase (see, page 1289, second column). Oxidation of uric acid

to allantoin is catalyzed by urate oxidase (see abstract). Increased uric acid level, due to lack of this enzyme in man can lead to gouty arthritis (page 1288, column 2).

Applicants' claims are directed to 'tetrameric mammalian uricase, wherein at least about 90% is in tetrameric form'. This is interpreted here to mean that more than 90% may also be present in the tetrameric form. More than 90% may also mean 100% or homogenous preparation. Therefore, the homogenous preparations of porcine or murine tetrameric uricase comprises the at least about 90% tetrameric form of mammalian uricase claimed. The reference therefore anticipates the claims.

Applicants' arguments:

As far as the rejection is concerned the Applicants find the anticipation rejection legally and factually baseless. Citing MPEP § 707.07(f) (February 2003), argue that where the Applicants traverse any rejection, the examiner should, if he or she repeats the rejection, take note of Applicants arguments and answer the substance of it. Based solely on this reason, Applicants respectfully contend that the present anticipation rejection under 35 U.S.C. 102(b) is improper, and should be withdrawn.

Applicants are reminded that the basis of traversal be found in the art applied. Regarding the Applicants arguments being not addressed, it is unclear what arguments are being referred to, which were not addressed. Further, it is not important to address every point which does not have a bearing to advancing prosecution, and/or points already explained in the art rejection.

Applicants in explaining Lee et al., point that Examiner contends that Lee discloses the recombinant production of full length amino acid sequence of porcine Urate oxidase (uricase) which is tetrameric and is substantially pure. Mammalian uricase is disclosed as a tetramer with subunit size of 32,000 Daltons (page 1288, column 2,first paragraph after the abstract). The reference further teaches purification to **homogeneity** of Porcine and murine urate

oxidase (see, page 1289, second column). Applicant respectfully disagrees with this interpretation for the following reasons.

Lee does not expressly disclose the purification of tetrameric mammalian uricase as recited by the claim of the present application. This reference only indicates *in passing* that the porcine liver and murine urate oxidase were purified to homogeneity. The reference does not indicate that at least 90% of the purified uricase was in tetrameric form. Indeed, the reference does not indicate in what form the purified uricase was, let alone that at least about 90% of it was in a tetrameric form.

From the article [Lee et al.] and from the clear explanation, it is amply clear that the art as applied anticipates the claims. First of all, the art cited clearly points to the fact that the mammalian uricase is disclosed as a tetramer with subunit size of 32,000 Daltons (page 1288, column 2,first paragraph after the abstract). This is also well documented in Applicants' own specification on page 3, line 15, citing Wu et al. [PNAS USA 86: 9412-9416, 1989].

Regarding Applicants' arguments that Lee's reference only indicates *in passing* that the porcine liver and murine urate oxidase were purified to homogeneity is without basis, and is distorting the facts presented in a well known and reputed scientific journal such as 'Science'. Further, as explained in the 102 rejection, at least 90% of the uricase was in tetrameric form, is encompassed by the homogeneous preparation, and is no different than what is claimed.

Applicants citing Conley et al. [Preparative Biochemistry 9:197-203 (1979)] argue that Conley report that the 'enzyme is homogeneous upon polyacrylamide gel electrophoresis in the presence of Sodium dodecyl sulfate [see Conley at p. 201]. Applicants further argue that one of ordinary skill in the art would immediately recognize, the conditions of SDS/PAGE employed by Conley (and therefore Lee) dissociate any uricase tetramer that might be present into the smaller 32-33 kDa monomeric subunits. As disclosed in the

present specification at page 16, lines 5-7, tetrameric uricase is 140 kDa protein. Hence, Conley (and therefore Lee) clearly is identifying monomeric forms of uricase, rather than tetrameric forms of uricase.

Applicants' explanation is not found persuasive because – in a denaturing gel such as SDS/PAGE, only the subunit form of the uricase is evident. Since all the 4-subunits are of the same size, the uricase appears/migrate as a single band on a SDS/PAGE. Since each subunit is approximately 32-33kDa, the native tetrameric form of the uricase in question would be 33X4=132 kDa, which is good estimate for molecular weight determination, and is within a reasonable range to that disclosed by the Applicants. Therefore, the homogeneous preparation of Lee et al. is not distinct to that claimed by the Applicants. No inherency argument is deemed necessary, because Conley's work further support Examiner's use of Lee et al. in 102 rejection.

Applicants' attention is also drawn to Conley et al. [Biochem. J (1980) 187, 727-732, IDS], at page 727, column 1, lines 1-3, where Uricase from pig liver consists of four apparently identical subunits. Table 2. further teaches the physical properties of pig uricase and define the molecular weight to be 125,000, with the subunit size of 32,000. Four identical subunits as defined by the Conley reference (1980) will further clarify that the uricase is tetrameric [four subunits].

Declaration of Merry R. Sherman Under 37 C.F.R. 1.132 (Arguments)

Applicants' support their conclusion by the data presented in the "Declaration of Merry R. Sherman Under 37 C.F.R. 1.132", and argue that these data clearly show that isolated preparations of natural and recombinant uricase, such as those prepared by the methods of Lee, contain multiple forms of the uricase, including Octobers and larger aggregates. Applicants further argue that as 'shown in Figures 1 & 2 (top panel) of the Sherman declaration,

the Octobers and larger aggregates (or non-tetrameric) account for greater than about 10% of the uricase present in these preparations.

This is contrary to Applicants' language in claim 50 (as previously presented), wherein the claim recites 'less than about 10%..in non-tetrameric form' (*see* Applicants' response, page 8, lines 10-18). This is further complicated by Applicants statement in the preceding paragraph (*see* Applicants' response, page 8, lines 3-9), wherein the non-tetrameric aggregated form of the enzyme present in such 'purified' preparations varies from more than 10% to about 80%. Therefore, base upon the diverse range of aggregations as a result of mammalian uricase purification, reported in the instant specification and the declaration of Merry R. Sherman, it is quite clear that there is enormous variations in the composition of uricase purified depending upon perhaps the buffers, dilutions, source and so on, and that the aggregation is the inherent property of the enzyme or that the different forms of the uricase (tetrameric or non-tetrameric) may aggregate differently. Therefore the added limitation of 'less than about 10% of said uricase is in a non-tetrameric aggregated form' is neither well supported nor carry weight to the patentability of the claims. The rejection under 35 U.S.C. 102(b) is therefore maintained.

New arguments: It is further noted that 'Figures 1 & 2 (top panel)' of the Sherman declaration, the Octobers and larger aggregates (or non-tetrameric) account for greater than about 10% of the uricase present in these preparations. There is no figure legend to describe the 3 different elution profiles in Figure 1 or several different elution profiles of Figure 2. It is impossible to determine if the uricase preparation is at least 90% in tetrameric form and at least 10% in non-tetrameric aggregated form. The HPLC on Superdex 200 of unfractionated PKS uricase (load) profile covers about 13 fractions. It is not clear if this is the entire profile of what was loaded on to the

column or is it a portion of the profile? It is further confusing that the unfractionated load is eluted in the same fraction as the Tetramer (*see* Figure 1, for example, of US Patent 6,783,965. It will be interesting to know how the percentages were calculated. The % calculation of tetrameric or non-tetrameric uricase appears to be random and with no clear-cut basis for these estimates. This is further reason to believe that % limitations in the claims of 'at least 90% of the uricase is in tetrameric form and less than about 10% of said uricase is in a non-tetrameric aggregated form' is neither well supported nor carry weight to the patentability of the claims.

Further, it should be noted that Figures 1 and 2 are **not part** of the original disclosure of the instant application. These Figures are part of US Patent 6,783,965.

7. ***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 50-59 are rejected under the judicially created doctrine of double patenting over claims 1-30 of U. S. Patent No. **6783965** since the claims, if allowed, would improperly extend the "right to exclude" already granted in the patent. This is revised double patenting rejection, since the allowed claims are

now patented and the Examiner has access to the patented claims, unlike the prior allowed claims. Applicants prior arguments presented are moot in view of this revised rejection. In view of this revised rejection, this office action is made non-final.

The subject matter claimed in the instant application is fully disclosed in the patent and is covered by the patent since the patent and the application are claiming common subject matter, as follows:

Applicants product or composition claims to mammalian uricase in this application differ in scope to patented claims directed to mammalian uricase containing at least 20% of uricase in the tetrameric form as compared to at least 90% of uricase in tetrameric form [instant claims], the instant claims being encompassed by the patented claims. The instant claims are a species of the patented genus claims, are therefore, anticipatory.

The rejection is maintained, since Applicants requested that this rejection be held in abeyance until subject matter that is otherwise patentable is identified.

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tekchand Saidha (Ph.D.) whose telephone number is (571) 272-0940. The examiner can normally be reached on Monday-Friday from 8:15 am to 4:45 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy, can be reached at (571) 272-0928. The fax phone number for this Group in the Technology Center is 703 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is 571 272-1600.

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November 30, 2005